PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P 66936	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No PCT/EP2004/011570	International filing date *(day/month/year)* 14.10.2004	Priority date *(day/month/year)* 14.10.2003
International Patent Classification (IPC) or national classification and IPC C12N5/06, A61K35/18, A61K35/28		
Applicant UNIVERSITÄTSKLINIKUM HAMBURG-EPPENDORF et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet
3. This report is also accompanied by ANNEXES, comprising:
   a ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets. as follows:
      ☐ sheets of the description claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed. as indicated in item 4 of Box No I and the Supplemental Box.
   b ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.05.2005	07 12.2005
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Renggli-Zulliger, N Telephone No +49 89 2399-7482

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No
PCT/EP2004/011570

Box No. I Basis of the report

1 With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))
- ☐ publication of the international application (under Rule 12 4)
- ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-26 as originally filed

Sequence listings part of the description, Pages

1-10 as originally filed

Claims, Numbers

1-36 received on 28.11.2005 with letter of 28 11 2005

Drawings, Sheets

1/4-4/4 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:
- ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:
- ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-36
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-36
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-36
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 99/61588 A (OSIRIS THERAPEUTICS INC) 2 December 1999 (1999-12-02)

D2: PEI XUETAO: "Stem cell engineering:The new generation of cellular therapeutics" INTERNATIONAL JOURNAL OF HEMATOLOGY SUPPL.I, vol. 76, August 2002 (2002-08), pages 155-156, XP009042425

D3: OSAWA M ET AL: "Long-term lymphohematopoietic reconstitution by a single CD34 low/negative hematopoietic stem cell" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 273, no. 5272, 12 July 1996 (1996-07-12), pages 242-245, XP002097289 ISSN: 0036-8075

D4: JIANG YUEHUA ET AL: "Pluripotency of mesenchymal stem cells derived from adult marrow" NATURE (LONDON), vol. 418, no. 6893, 4 July 2002 (2002-07-04), pages 41-49, XP001204372 ISSN: 0028-0836

D5: REYES MORAYMA ET AL: "Origin of endothelial progenitors in human post-natal bone marrow" BLOOD, vol. 98, no. 11 Part 1, 16 November 2001 (2001-11-16), page 821a, XP002313288 & 43RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY, PART 1; ORLANDO, FLORIDA, USA; DECEMBER 07-11, 2001 ISSN: 0006-4971

D6: PEI X: "Who is hematopoietic stem cell: CD34+ or CD34-?" INTERNATIONAL JOURNAL OF HEMATOLOGY. DEC 1999, vol. 70, no. 4, December 1999 (1999-12), pages 213-215, XP009042521 ISSN: 0925-5710

D7: HU YING ET AL: "Transplantation of mesenchymal stem cells followed by G-CSF injection can reconstitute hematopoiesis of lethally irradiated BALB/C mice" BLOOD, vol. 98, no. 11 Part 2, 16 November 2001 (2001-11-16), page 316b, XP009042610 & 43RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY, PART 2; ORLANDO, FLORIDA, USA; DECEMBER 07-11, 2001 ISSN: 0006-4971

D8: WO 03/070922 A (HA CHUL-WON ; YANG SUNG-EUN (KR); YANG YOON-

SUN (KR); MEDIPOST CO LTD) 28 August 2003 (2003-08-28)

Novelty (Article 33(1) and (2) PCT) and Inventive step (Article 33(1) and (3) PCT)

The present application refers to a method of *in vitro* culturing and differentiating mesenchymal stem cells that are CD34-negative, CD105, CD59, CD90, CD13 and MHC I positive after at least one passage in culture with growth factors in order to produce blood products. None of the cited prior art documents disclose nor suggest that these mesenchymal cells could be differentiated *in vitro* into blood products. Therefore, the subject-matter of claims 1-7,19-36 is novel and inventive in view of the cited prior art.

The subject-matter of claims 8-18 that has been reformulated in medical use type claims is considered novel for the following reasons:
Although it is a product-by-process type formulation, the present method of claims 1-7 gives a blood product that has different characteristics (i.e. its use for allogenic patients) from normal blood products derived from the blood of donors that have been purified using standard physico-chemical procedures

Re Item VIII
Certain observations on the international application

The correct formulation in "Swiss-type claims" according to the standard of the EPO will be examined in the regional phase.